REMARKS

Claims 7, 11-13, 26, and 28-31 are currently pending in the application. Claims 12-13 stand withdrawn as being directed to a nonelected species. New claims 29-31 have been added. Support for the new claims may be found on page 16, paragraph 4, lines 3-4 of the PCT specification as filed.

As a preliminary matter, upon further review of the prior art and the present data, Applicants' representative acknowledges and regrets a calculation error in the previous response regarding the comparison between the synergistic effects of the sequential administration procedure disclosed in the application and the combined administration procedure of the prior art. Thus, Applicant corrects the previous assertion of a 10-40 fold synergistic effect for the claimed method to a 3.3 to 16-fold synergistic effect on apoptosis of the treated cells based on Example 2 of the present application. Nevertheless, Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

In the Office Action, claims 7, 11, 26, and 28 stand rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Jagdev *et. al.* (*British Journal of Cancer,* 84:1126-1134, 2001). The Office asserts that the prior art reference teaches treatment of breast cancer with a combination of Paclitaxel and Zoledronic acid, which results in synergistic effects on breast cancer cell number and apoptosis. The Office further asserts that Applicants have failed to show the synergistic effect over a wide range of concentrations and that the synergistic effects of the two experiments shown by the Applicants are not much different from the ones taught in the prior art. Applicants respectfully traverse this rejection in view of the lack of a reasonable expectation that the results in Jagdev could be obtained with the presently claimed methods and the surprising and unexpected results of the claimed sequence of administration.

Support for this reasoning is set forth in the attached declaration of one of the inventors, Dr. Ingunn Holen, an experienced oncology researcher (Declaration, ¶ 1). In her declaration, Dr.

Holen describes the difference between the instant sequential Paclitaxel (PAC) and Zoledronic acid (ZOL) administration studies and the combination ZOL and PAC studies conducted by Jagdev *et. al.*

First, the concentration of ZOL (10 μM and up) and incubation period of 72 hours for ZOL and PAC taught by Jagdev *et al.* are not clinically relevant. As noted by Dr. Holen and shown by a literature review article (Diel *et al.* "Adverse Effects of Bisphosphonates," *J. Support. Oncol.* 5: 475-82, 2007; submitted herewith), due to well-known renal toxicity, acute phase reactions, and osteonecrosis of the jaw, ZOL is typically administered for cancer treatment in small carefully controlled doses widely spaced in time: e.g., by IV infusion for 15 minutes at a dose of 4 mg/patient no more often than once every 3-4 weeks. (Declaration, ¶ 2.) Following IV infusion, ZOL is known to remain in the plasma for no more than a few hours before being excreted or localizing to the bone. (*Id.*) Hence, repeated and prolonged infusion periods of zoledronic acid would be required to reproduce the 72 hours exposure tested in the Jagdev reference and such an exposure is not achievable in clinical practice due to the toxicity of zoledronic acid. (*Id.*) By definition, therefore, since the concentrations and exposure times of at least the ZOL disclosed by Jagdev *et al.* are not clinically achievable, they are not and cannot be translated into an effective amount as recited by the claimed methods.

By contrast with the cited reference, the claimed method uses clinically relevant concentrations and exposure times of ZOL and PAC. As explained by Dr. Holen, the present application discloses a first experiment in which ZOL (25 uM) was administered (after PAC, 2 nM) for a significantly shorter time (1 hour) than in Jagdev et al. (Declaration, ¶ 3) This is important as ZOL is typically administered to a cancer patient in short (15 minute) IV infusions spaced at least 3-4 weeks apart. (*Id.*) As noted above, after such an infusion, ZOL localizes to the bone or is excreted and therefore cancer cells (such as breast cancer cells) are exposed to ZOL only briefly. The 1 hour exposure is therefore far closer to what happens in the clinic than the 72 hour exposure employed by Jagdev. The fact that an exposure time for ZOL of only 1.3%

as long as that used in the prior art reference still resulted in a synergistic effect demonstrates proof of principle for this clinically relevant exposure time.

In a second experiment (also described at ¶ 3 of the Declaration), a clinically relevant 1 uM concentration of ZOL was administered to the breast cancer cells for a clinically relevant 1 hour period after the cells were exposed to PAC (2 nM, 4 hours). A synergistic effect on the apoptosis of the breast cancer cells (4.1%) was observed compared to either drug alone. As explained by Dr. Holen at ¶ 4 of the Declaration, the concentration of ZOL (1 μM) is quite similar to the peak plasma concentration of ZOL, which is 1-2 uM following a 4 mg IV infusion, before it is excreted or localizes to bone. As noted above, the 1 hour exposure period is also clinically relevant as it tracks more closely the *in vivo* exposure time of cancer cells in a patient to a standard dose of ZOL. *Id.* Further, Dr. Holen describes that it was surprising to her that such a low, clinically relevant exposure to ZOL sequentially with PAC could produce the relatively large synergistic effects on apoptosis which were observed. (Declaration, ¶ 5.) Applicants respectfully submit that such an outcome could not reasonably be expected based on Jagdev's disclosure of combined administration of PAC and ZOL where the PAC was administered for 18 times as long and ZOL was administered at an order of magnitude higher concentration and for 72 times as long as in the present application.

On a final note, Applicants submit that the Examiner's comment that Applicants have failed to show the synergistic effect over a wide range of concentrations has no bearing on the obviousness or patentability of the claimed methods. As shown above, Applicants tested the sequential administration of PAC and ZOL at clinically relevant concentrations and exposure times whereas Jagdev *et al.* did not. Indeed, testing at, e.g., higher concentrations as performed by Jagdev *et al.* is not necessary in view of the limited range of ZOL doses used clinically. In fact, during clinical trial of zoledronic acid, "renal damage and creatinine level elevation were even observed in the phase III trial of this drug, especially at the 8-mg dose tested initially. On the recommendation of a renal safety committee, the 8-mg dose of zoledronic acid was abandoned, and the infusion time was extended from 5 to 15 minutes." (Diel at p. 476, 2nd

column.) Clearly, 4 mg zoledronic acid infused by IV over 15 minutes is the standard effective amount for this agent and Applicant's test conditions reproduce this dosage closely. Moreover, Applicants did in fact test the sequential administration of PAC and ZOL at 25 uM ZOL, a much higher than the clinically relevant concentration, and still demonstrated the synergistic effect. Hence, Applicants respectfully submit that the doses tested are appropriate to support the claimed methods and that there is no deficiency with respect to obviousness or any other aspect of patentability.

Because the amounts and exposure times of ZOL and PAC set forth in Jagdev *et al.* are not effective amounts within the meaning of the claims, and because the skilled artisan would not have had a reasonable expectation of success in obtaining the present synergistic results after modifying the procedures of Jagdev *et al.* to provide the claimed methods, and because the results obtained with the claimed methods are in fact surprising and unexpected, Applicant submits that the claimed methods are not obvious over the cited reference. Accordingly, Applicants respectfully request that the present rejection under § 103(a) be withdrawn.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. Should any issues remain open after consideration of the present amendment and reply, the Examiner is invited to contact the undersigned so that a prompt disposition of the application may be achieved.

Respectfully submitted,

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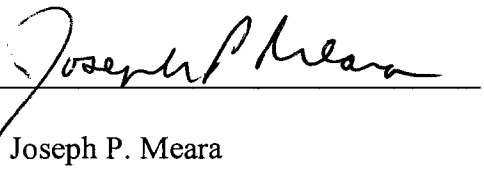
By 

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